## REMARKS

**Status.**

Claims 1-13 are pending with entry of this amendment, claims 14-28 being cancelled and no claims being added herein. Claims 1, 2, 3, 4, 5, and 6 are amended herein. These amendments introduce no new matter. Support is replete throughout the specification (*e.g.*, page 3, lines 20-26, page 10, line 22 through page 12, line 20, the claims as filed, *etc.*).

The amendments provided herein are made solely to address rejections under 35 U.S.C. §112 and not to address rejections in light of the prior art. Applicants expressly state for the record that the amendments do not preclude the use of the Doctrine of Equivalents as applied by an appropriate court. Applicants are clearly entitled, absent amendments in view of the prior art, to assert claims issue from this application against an infringer under the Doctrine of Equivalents (*see, e.g. Warner-Jenkinson Co. v Hilton Davis Chem.* 41 USPQ2d 1865 (1997), *Litton Systems Inc. v Honeywell Inc.* 46 USQ2d 1341 (Fed. Cir. 1998)).

Claim 6 was objected to because of a typographical error. Claims 1-13 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-27 of U.S. Patent 5,723,291. Claims 1-13 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. Claims 1-5, 8, and 10-11 were rejected under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent 5,723,291 (Kushner *et al.*). Claims 1-5, 8, and 10-11 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Gaub *et al.* (1990) *Cell,* 63: 1267-1276. Claims 1-5, 8, and 10-11 were rejected under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent 5,639,592 (Evans *et al.*). Claims 1-2, 4, 8, and 10-11 were rejected under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent 6,004,748 (Pfahl *et al.*). Applicants respectfully traverse.

**Election/Restriction.**

Applicants note that the restriction requirement is made final. Accordingly non-elected claims 14-28 are canceled with entry of this amendment. Please note, however, that Applicants reserve the right to file subsequent applications claiming the canceled subject matter and the claim cancellations should not be construed as abandonment or agreement with the Examiner's position in the Office Action.

**Claim Objections.**

Claim 6 was objected to because of a typographical error where line 3 recited "a an". This has been corrected with entry of this amendment thereby obviating this objection.

**Double Patenting.**

Claims 1-13 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-27 of U.S. Patent 5,723,291. Applicants respectfully traverse.

The Examiner is respectfully reminded that a double-patenting rejection is essentially an obviousness rejection **in light of the claims** of one or more earlier patents. As stated by the Federal Circuit:

> A double patenting of the obviousness type rejection is "analogous to [a failure to meet] the non-obviousness requirement of 35 U.S.C. §103," except that **the patent principally underlying the double patenting rejection is not considered prior art**. In *re Longi,* 225 USPQ 645 (Fed. Cir. 1985) *n.4, citing In re Braithwaite* 154 USPQ 29, 34 (CCPA 1967)

The inquiry is whether or not the claimed invention is patentably distinct (nonobvious) from the cited claims and references and this is evaluated under the body of law pertaining to the analysis of obviousness under 35 U.S.C. §103(a).

The Examiner is reminded that an obviousness rejection requires a teaching or suggestion to modify the references in the manner indicated by the Examiner. As stated by the Court of Appeals for the Federal Circuit:

> Our case law makes clear that the best defense against hindsight-based obviousness analysis is the rigorous application of the requirement for a showing of a teaching or motivation to combine the prior art references. See Dembiczak, 175 F.3d at 999, 50 USPQ2d at 1617. **"Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight." Id.** [emphasis added] *Ecolochem, Inc. v Southern-California Edison Company,* __ USPQ2d ___ (Fed. Cir. 2000)

* * *

> The mere fact that the prior art may be modified in the manner suggested by the Examiner **does not** make the modification obvious unless the prior art suggested the desirability of the modification. [emphasis added] *In re Fritch*, 23 USPQ 2d 1780, 1783-1784 (Fed. Cir. 1992)

The presently pending claims incorporate a limitation not recited in the claims of the '291 patent. In particular, presently pending claim 1 recites

> a) providing a first cell containing an estrogen receptor, a **cognate receptor for said nuclear transcription factor ligand**, and a promoter comprising an AP-1 site which regulates expression of a first reporter gene;

and

> c) detecting expression of said first reporter gene, whereby an alteration in expression of said first reporter gene, as compared to expression of said first reporter gene in the absence of said transcription factor ligand, **indicates that said nuclear transcription factor ligand modulates estrogen activation at an AP-1 site.**

while claim 1 of the '291 patent provides:

> a) providing a cell comprising AP1 proteins, an estrogen receptor, and a construct comprising a promoter comprising an AP1 site which regulates expression of a reporter gene;

and

> c) detecting the expression of said reporter gene wherein enhanced expression of said reporter gene indicates that said test compound has agonistic estrogenic activity mediated through an indirect estrogen response.

The Examiner has failed to articulate with particularity a teaching or suggestion of the presently claimed method. The Examiner has offered no indication where claims 1-27 of the '291 patent teach or suggest a cognate receptor for a nuclear transcription factor as recited in act "a" of presently pending claim 1. Similarly, the Examiner offered no indication where claims 1-27 of the '291 patent teach or suggest that a nuclear transcription factor ligand can modulate estrogen activation at an AP-1 site.

Stating that the cells of the '291 patent can be used for comparison to detect responses is at best taking the present inventor's own disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight." This is an insufficient

and improper basis for an obviousness rejection. The Examiner has failed to make his *prima facie* case and, accordingly, the obviousness type double patenting rejection in light of the '291 patent should be withdrawn.

**35 U.S.C. §112, Second Paragraph.**

Claims 1-13 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for the reasons summarized below.

Claim 3 was allegedly confusing and ambiguous because claim 2 further comprises a second cell from the method of claim 1, but then the claim 3 limitation is directed to the first and second cell being the same cell. A similar rejection was made of claim 5. Claims 2 and 4 are amended herein to eliminate the reference to a "second" cell. Claims 2 and 4 are therefore directed to the methods further comprising providing a cell containing the recited elements and dependent claims 3 and 5 clarify that the cell can be the same cell as in claim 1 or a different cell. Applicants believe the amendment obviates these rejections.

Claims 7, 9, 12, and 13 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite because, according to the Examiner, there is insufficient antecedent basis for the limitation "said cognate receptor". Claim 1 is amended herein to recite "a cognate receptor" thereby providing sufficient antecedent basis and obviating these rejections.

Claims 1-13 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being incomplete for failure to recite a critical step. In particular, the Examiner argued that claim 1 failed to provide an act whereby the transcription factor ligand specifically modulates estrogen activation at an AP-1 site. The Examiner further alleged that there is no control experiment step to provide specificity to the purpose stated in the preamble.

Claim 1 is amended herein to recite:

> c) detecting expression of said first reporter gene**, whereby an alteration in expression of said first reporter gene, as compared to expression of said first reporter gene in the absence of said transcription factor ligand, indicates that said nuclear transcription factor ligand modulates estrogen activation at an AP-1 site.**

In view of this amendment the pending claims unambiguously relate the acts recited in the method to the purpose stated in the preamble. This rejection should therefore be withdrawn.

In view of the foregoing, Applicants believe the rejections of claims 1-13 under 35 U.S.C. §112, second paragraph, are obviated and request that these rejections be withdrawn.

**35 U.S.C. §102.**

Claims 1-5, 8, and 10-11 were rejected under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent 5,723,291 (Kushner *et al.*). Claims 1-5, 8, and 10-11 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Gaub *et al.* (1990) *Cell,* 63: 1267-1276. Claims 1-5, 8, and 10-11 were rejected under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent 5,639,592 (Evans *et al.*). Claims 1-2, 4, 8, and 10-11 were rejected under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent 6,004,748 (Pfahl *et al.*). Applicants respectfully traverse.

The Examiner is respectfully reminded that anticipation requires that "all limitations of the claim are found in the reference, or 'fully met' by it." *Kalman v Kimberly-Clark Corp.*, 218 USPQ 781, 789 (Fed. Cir. 1983). Applicants explain below that the cited references fails to provide all the elements of the presently claimed invention.

**U.S. Patent 5,723,291 (Kushner *et al.*).**

The 5,723,291 patent fails to disclose a method in which a cell containing a cognate receptor for a nuclear transcription factor ligand is contacted with a nuclear transcription factor. The Examiner asserts that "fos and jun are nuclear receptors and ligands because they are transcription factor sand they bind to each other." Applicants disagree with the Examiner's characterization of either fos or jun as a transcription factor receptor noting that this is not conventional usage of these terms in the art.

Nevertheless, assuming, *arguendo,* that the Examiner's characterization is correct, Applicants note that pending claim 1 expressly recites:

b) contacting said first cell with said transcription factor ligand . . .

In light of the Examiner's interpretation, to anticipate the pending claims the '291 patent must disclose a method that involves contacting the cell with either fos or jun (the Examiner does not identify which he regards as the receptor and which the ligand). The Examiner has failed to show where the '291 patent teaches contacting the cell with fos or jun and has therefore failed to make his *prima facie* case. Dependant claims 2-5, 8, and 10-11 incorporate all the

limitations of independent claim 1 and are similarly not anticipated by the '291 patent. Accordingly, the rejection of claims 1-5, 8, and 10-11 under 35 U.S.C. §102(e) should be withdrawn.

**U.S. Patent 5,639,592 (Evans *et al.*).**

The 5,639,592 patent fails to disclose a method having all of the elements of the presently claimed methods. Presently pending claim 1 recites:

1) A first cell containing an estrogen receptor;

2) A first cell containing. . . a cognate receptor for said nuclear transcription factor ligand;

3) Contacting said first cell with said transcription factor ligand; and

4) Contacting said first cell with . . . a compound having AP-1 mediated estrogenic activity.

The '592 patent fails to disclose an assay method in which a cell is contacted with **both** a transcription factor ligand, and a compound having AP-1 mediated estrogenic activity. AP-1 mediated estrogenic activity is defined in the specification as "activation of a gene under the control of an AP-1 site (also referred to as an AP-1 response element) mediated by the interaction of a nuclear transcription factor with the AP-1 site." (page 7, lines 25-27).

According to the Examiner jun or fos are nuclear transcription factors (*see* Office Action, page 8, lines 4-6). Under this interpretation, to anticipate the presently pending claims, the '592 patent must disclose a method in which a cell is contacted with both jun or fos and with an agent that activates transcription of a gene under control of an AP-1 site. The '592 fails to disclose such a method and accordingly, the rejection of claims 1-5, 8, and 10-11 under 35 U.S.C. §102(e) in light of the '592 patent should be withdrawn.

Should the Examiner desire to maintain his rejection under §102(e) Applicants respectfully request that he identify with particularity the correspondence of each element in the pending claims with corresponding elements in a method disclosed in the '592 patent.

**U.S. Patent 6,004,748 (Pfahl *et al.*).**

The 6,004,748 patent also fails to anticipate the presently pending claims. As indicated above, the presently pending claim 1 recites

1) A first cell containing an estrogen receptor;

2) A first cell containing. . . a cognate receptor for said nuclear transcription factor ligand;

3) Contacting said first cell with said transcription factor ligand; and

4) Contacting said first cell with . . . a compound having AP-1 mediated estrogenic activity.

The '748 patent fails to disclose a method that involves contacting a cell with a compound having AP-1 mediated estrogenic activity (*e.g.* β-estradiol) and with a transcription factor ligand. Lacking such a teaching, the '748 patent fails to provide a limitation of presently pending independent claim 1 or dependent claims 2, 4, 8, and 10-11. The rejection of these claims under 35 U.S.C. §102(e) should therefore be withdrawn. Should the Examiner desire to maintain his rejection under §102(e) Applicants respectfully request that he identify with particularity the correspondence of each element in the pending claims with corresponding elements in a method disclosed in the '748 patent.

**Gaub *et al.* (1990) *Cell*, 63: 1267-1276.**

Gaub *et al.* also fails to anticipate the presently claimed invention. The Examiner is reminded that claim 1 expressly recites:

> a) providing a first cell containing an estrogen receptor, a **cognate receptor for said nuclear transcription factor ligand**, and a promoter comprising an AP-1 site which regulates expression of a first reporter gene;

Contrary to the Examiner's assertion, Gaub *et al.* does not teach a cell comprising an estrogen receptor **and** a cognate receptor for said nuclear transcription factor ligand.

The Examiner is reminded that unless otherwise defined, the general rule is that:

> [T]erms in the claim are to be given their **ordinary and accustomed meaning**. [emphasis added] *See Johnson Worldwide Associates Inc. v Zebco Corp.* 50 USPQ2d 1607, 1610 (Fed. Cir. 1999) citing *Renishaw*, 158 F.3d at 1249, 48 USPQ2d at 1121; *York Prods., Inc. v. Central Tractor Farm & Family Ctr.*, 99 F.3d 1568, 1572, 40 USPQ2d 1619, 1622 (Fed. Cir. 1996).

In the instant case, the term the term "cognate receptor" is defined as "**a receptor** of the type that is typically bound by the transcription ligand in question." (*see* specification page 6, lines

13-14). The term "receptor", however, is undefined and must be interpreted in accordance with ordinary and accustomed usage.

Contrary to the Examiner's assertion, fos and jun **are not** described as cognate receptors for a nuclear transcription factor ligand. To the contrary, fos and jun are typically referred to simply as transcription factors. Binding of fos to jun is not characterized as a receptor binding its cognate substrate, but rather is characterized as heterodimerization to form the AP-1 transcription factor:

> Fos: <oncogene> An oncogene, identified in a mouse osteosarcoma, **encoding a transcription factor**. The product of this oncogene works with the product of another oncogene, the jun oncogene, to abnormally change the rate of transcription of certain other genes. **Fos and jun proteins dimerise** via a leucine zipper to form the AP 1 transcription factor. [emphasis added] (*see* CancerWeb Online Medical Dictionary, http://www.graylab.ac.uk/cgi-bin/omd?action=Home&query=)

As jun and fos are not cognate receptors for a nuclear transcription factor ligand the Gaub *et al.* reference fails to disclose a cell comprising both an **estrogen receptor and a cognate receptor** for a transcription factor ligand. Claim 1 is therefore not anticipated by Gaub *et al.* and consequently, dependent claims 2-5, 8, and 10-11, which incorporate all the limitations of claim 1 are also not anticipated. Accordingly the rejection of claims 1-5, 8, and 10-11 under 35 U.S.C. §102(b) in light of Gaub *et al.* should be withdrawn.

Should the Examiner desire to maintain his characterization of fos or jun as a receptor for a nuclear transcription factor ligand, the Examiner is respectfully invited to identify a reference in the art to fos or jun as receptors for a nuclear transcription factor ligand.

In view of the foregoing, Applicant believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (415) 217-6021.

Respectfully submitted,

Tom Hunter
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Encl: 1) Petition for 3 month extension of time.
2) Change in correspondence address.

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## APPENDIX I

## CLAIMS PENDING IN 09/103,365 WITH ENTRY OF THIS AMENDMENT

1. (Once amended) A method of screening a nuclear transcription factor ligand for the ability to modulate estrogen activation at an AP-1 site, said method comprising the steps of:

a) providing a first cell containing an estrogen receptor, a cognate receptor for said nuclear transcription factor ligand, and a promoter comprising an AP-1 site which regulates expression of a first reporter gene;

b) contacting said first cell with said transcription factor ligand and with a compound having AP-1 mediated estrogenic activity; and

c) detecting expression of said first reporter gene, whereby an alteration in expression of said first reporter gene, as compared to expression of said first reporter gene in the absence of said transcription factor ligand, indicates that said nuclear transcription factor ligand modulates estrogen activation at an AP-1 site.

2. (Once amended) The method of claim 1, further comprising the steps of:

d) providing a cell containing an estrogen receptor, a cognate receptor for said nuclear transcription factor ligand, and a promoter comprising an estrogen response element (ERE) that regulates expression of a second reporter gene;

e) contacting said cell with said transcription factor ligand and with said compound having AP-1 mediated estrogenic activity; and

f) detecting expression of said second reporter gene.

3. (Once amended) The method of claim 2, wherein said first cell and the cell containing the estrogen response element that regulates expression of a second reporter gene are the same cell.

4. (Once amended) The method of claim 1, further comprising the steps of:

d) providing a cell containing a cognate receptor of said transcription factor ligand, and a promoter comprising a response element for said cognate receptor that regulates expression of a second reporter gene;

e) contacting said cell with said transcription factor ligand and with said compound having AP-1 mediated estrogenic activity; and

f) detecting expression of said second reporter gene.

5. (Once amended) The method of claim 4, wherein said first cell and the cell containing a cognate receptor of said transcription factor ligand are the same cell.

6. (Once amended) The method of claim 1, wherein said nuclear transcription factor ligand is selected from the group consisting of a glucocorticoid, a progestin, vitamin D, retinoic acid, [a] an androgen, a mineralcorticoid, and a prostangladin..

7. The method of claim 1, wherein said cognate receptor is selected from the group consisting of an estrogen receptor, a glucocorticoid receptor, a progestin PR-A receptor, and progestin PR-B receptor, androgen receptor, a mineralcorticoid receptor, and a prostaglandin receptor.

8. The method of claim 1, wherein said cell expresses said estrogen receptor from a heterologous DNA.

9. The method of claim 1, wherein said cell expresses said cognate receptor from a heterologous DNA.

10. The method of claim 1, wherein said cell expresses an AP-1 protein from a heterologous DNA.

11. The method of claim 10, wherein said AP-1 protein is c-jun.

12. The method of claim 1, wherein said nuclear transcription factor is a progestin; and said cognate receptor is a progestin receptor.

13. The method of claim 1, wherein said nuclear transcription factor is a glucocorticoid and said cognate receptor is a GR receptor.